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Nonclassic Measles Infections in an Immune Population Exposed to Measles During a College Bus Trip

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This study investigated the frequency of mild or asymptomatic measles infections among 44 persons exposed to a student with measles during a 3-day bus trip using two buses. Questionnaires and serum samples were obtained 26–37 days after the trip. All participants had detectable measles-neutralizing antibodies, and none developed classic measles symptoms. Ten persons (23%) were IgM positive for measles, indicating recent infection. Among previously vaccinated IgM-negative persons, those who rode on bus A with the index case-patient had significantly higher microneutralization titers than those on bus B ($P = .001$), suggesting that some persons on bus A were infected but were IgM negative at the time of the study. Mild or asymptomatic measles infections are probably very common among measles-immune persons exposed to measles cases and may be the most common manifestation of measles during outbreaks in highly immune populations. ***J. Med. Virol. 56: 337–341, 1998.*** © 1998 Wiley-Liss, Inc.†

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INTRODUCTION

Measles is a significant cause of mortality for children in developing countries. The Pan American Health Organization is working toward eliminating measles from the Americas [de Quadros et al., 1996], and the World Health Organization is considering a program for the global eradication of measles. As vaccination coverage improves, however, it becomes increasingly important to understand the clinical and epidemiologic features of measles in highly immune populations. It is particularly important to understand how frequently mild or subclinical infections occur and whether they can contribute to the spread of measles.

It has long been recognized that measles virus can infect previously immune persons, producing classic symptoms of measles in some, and mild or no symptoms in others [Linnemann, et al., 1972; Chen et al., 1990; Edmonson et al., 1990; Cherry et al., 1972; Smith et al., 1982; Reyes et al., 1987; Huiss et al., 1997]. The estimated rates of mild or asymptomatic measles infections after exposure to measles cases are varied, however, in part because of different diagnostic techniques, different case definitions, or different types of exposure [Cherry et al., 1972; Linneman et al., 1972; Chen et al., 1990; Huiss et al., 1997]. In these studies, the rates of mild or asymptomatic infection were determined during outbreaks in which persons were likely to have had multiple exposures to measles cases. With increasing vaccination coverage in the United States, most measles cases now occur in isolation or as part of small outbreaks (all outbreaks had fewer than ten cases during 1997) [Centers for Disease Control and Prevention, 1998]. In this report, we describe our investigation to determine the rate of mild or asymptomatic measles infections among persons likely to have been exposed to one student with classic measles during a 3-day college-sponsored bus trip.

Institutional Review Board approval was received from Centers for Disease Control and Prevention. Informed consent was obtained from all participants.

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MATERIALS AND METHODS

Background

During May 1996, 94 college students, faculty, and relatives traveled for 3 days in two buses from southwestern Utah to a neighboring state to visit museums. Most persons traveled on the same bus throughout the trip, but could interact with persons on the other bus at other times, such as during meals, visits to museums, and at rest stops. On the first day of the trip, a student on bus A became ill with fever, cough, and coryza. Three days later, this student developed a generalized maculopapular rash and was subsequently confirmed by serologic studies to have measles. The student reported having been vaccinated previously with one dose of measles-containing vaccine (MCV). This case of measles occurred in the context of a countywide outbreak of more than 100 cases of measles, but was one of only four cases of measles at the college.

Epidemiologic Study

Including the index case-patient, 45 (48%) of the 94 persons on the trip agreed to participate in the study. Forty-nine persons were not enrolled for various reasons: One (2%) had been vaccinated with MCV within 60 days of the trip and was excluded; 38 (78%) could not be reached after three or more attempts; eight (16%) were contacted but had moved away for the summer (the investigation occurred during the last week of final exams); and two (4%) declined participation. Because the low enrollment rate was a result of the timing of the investigation rather than refusals to participate, it is unlikely to have biased the serologic results.

After obtaining informed consent from the participants, we collected demographic information, illness histories, and measles vaccination status. Vaccination status was confirmed, when possible, through vaccination cards, school records, medical records, or parental reports. We also collected a sample of blood by venipuncture to test for the presence of measles-specific antibodies.

Serologic Analyses

Serum specimens were tested for the presence of measles-specific IgM antibodies by using a previously described enzyme immunoassay that has been shown to be 96–97% sensitive [Erdman et al., 1991, 1993] and 99% specific [Hummel et al., 1992]. Measles-specific IgG antibodies were measured by using a previously described indirect EIA [Hummel et al., 1992]. Neutralizing antibody levels were measured by using a microneutralization (mNT) EIA [Erdman et al., 1991] and are reported as a reciprocal of end point dilutions between 1:5 and 1:640.

Case Definitions

Persons who were IgM positive were defined to have a recent measles infection. We defined a classic case of measles as a person with an illness that met the Centers for Disease Control and Prevention (CDC) clinical case definition (temperature > 38.3°C [101°F], generalized rash lasting at least 3 days, and at least one of the following: cough, coryza, or conjunctivitis [Centers for Disease Control, 1990]) and who was measles IgM-positive. A nonclassic case of measles was defined as a person with a recent measles infection indicated by the presence of measles IgM, but who did not meet the clinical case definition. These nonclassic cases were not reported as cases for the national notifiable diseases reporting system because they neither met the clinical case definition nor were clinically suggestive of measles (e.g., a rash illness).

We categorized participants into two groups: a natural infection group and a vaccinated group. The natural infection group included persons with histories of natural measles infection. All had been born before 1957, and only one reported receiving MCV. The vaccinated group included persons born after 1957 who had been vaccinated with MCV and reported never having had a natural measles infection. This vaccinated group also included two participants with unknown vaccination status who were born at a time when MCV was used routinely (i.e., 1975 and 1976), who had serologic evidence of measles immunity, and reported never having had clinical measles.

Data Analysis

We used two-tailed Fisher's exact tests and Mantel-Haenzsel chi square to compare categorical variables, and we used the exact Wilcoxon and stratified Wilcoxon rank sum tests to compare ordered variables.

RESULTS

Characteristics of Enrolled Subjects

The median age of the 44 participants exposed to the index case was 20.5 years (range 18–68 years; median ages on buses A and B were 19 and 22.5 years, respectively). Forty-one (93%) were Caucasian. Vaccination histories for the 33 persons with a history of previous vaccination were obtained from medical records (N = 2), vaccination cards (N = 20), school record (N = 1), parent report (N = 1), and self-report (N = 9). The average time since vaccination was 17.4 years (range .3–22.3 years). Twenty-six participants (59%) rode on bus A with the index case-patient. Twenty-five of the 26 participants on bus A were in the vaccinated group; 16 had received one dose of MCV, eight had received two doses of MCV, and one had an unknown vaccination history. Ten of the 18 passengers on bus B were in the natural infection group and eight were in the vaccinated group; among the persons in the vaccinated group, six had received one dose of MCV, one had received two doses of MCV, and one had an unknown vaccination history. The 44 study participants were enrolled a median of 30 days after the index case-patient developed a rash (range 26–37 days).

IgM Results

Overall, ten (23%) of the 44 participants tested IgM-positive against measles, and two persons (5%) had

TABLE I. Microneutralization Values for Persons on the Bus Trip Who Were Exposed to the Measles Case-Patient*

	Both buses			Bus A			Bus B		
Participants	No.	Median	Range	No.	Median	Range	No.	Median	Range
Overall	44[a]	80	5–⩾640	26[a]	320	40–⩾640	18	40	5–320
IgM+ persons	10	320	80–⩾640	7	⩾640	320–⩾640	3	160	80–320
IgM– persons	32	40	5–⩾640	17	160	40–⩾640	15	20	5–160
Natural infection group	11	80	10–320	1	80	NA	10	60	10–320
IgM+ persons	3	160	80–320	0	NA	NA	3	160	80–320
IgM– persons	8	40	10–160	1	80	NA	7	40	10–160
Vaccinated group*	33[a]	160	5–⩾640	25[a]	320	40–⩾640	8	20	5–40
IgM+ persons	7	⩾640	320–⩾640	7	⩾640	320–⩾640	0	NA	NA
IgM– persons	24	60	5–⩾640	16	240	40–⩾640	8	20	5–40

*NA, Not applicable.
[a]Includes two persons with borderline IgM results that are not displayed separately. Dilution series from 1:5 to 1:640.

borderline IgM values (Table I). None met the clinical case definition for measles. The two persons with borderline IgM results rode on bus A and are excluded from all direct comparisons of IgM-positive versus IgM-negative persons. The rates of IgM-positivity did not vary by prior immune status; three (27%) of 11 persons in the natural infection group were IgM positive compared with seven (21%) of 33 in the vaccinated group ($P = .48$). We next compared the proportions of IgM-positive persons for the two buses. On bus A, seven (27%) of 26 persons were IgM positive; four of these persons had been vaccinated once, and three had been vaccinated twice. On bus B, 3 (17%) of 18 persons were IgM-positive, all in the natural infection group. This difference in rates of IgM-positivity between the two buses was not statistically significant ($P = .29$), and the difference in rates of IgM-positivity by prior immune status was not statistically significant when controlling for bus ($P = .25$). The timing of the blood collection was similar for IgM-positive (median 30 days, range 29–31 days) and IgM-negative (median 30 days, range 26–37 days) persons ($P = .56$).

IgG and Neutralizing Antibody Results

Overall, 43 (98%) of the 44 persons were IgG positive by indirect EIA. The one IgG-negative person had a detectable mNT titer of 5 and was IgM-negative. All ten of the IgM-positive persons had absorbance readings with ratios of IgM to IgG of less than 1, consistent with a secondary or anamnestic response with a rapid rise in IgG antibodies [Erdman et al., 1993]. All 44 persons had detectable mNT titers, with a median titer of 80 (range 5 to ⩾640; Table I). IgM-positive persons had significantly higher mNT titers than IgM-negative persons, even after controlling for immune status ($P = .001$) and for bus ($P = .001$). In addition, persons on bus A (longer and more intense exposure to the index case) had significantly higher mNT titers than persons on bus B, even after controlling for previous immune and IgM status ($P < .0001$; $N = 42$; Table I). The difference in neutralizing antibody titers between persons on the two buses was greater among IgM-negative persons; vaccinated IgM-negative persons on bus A had significantly higher mNT titers than the comparable group on bus B ($P < .001$; $N = 24$). Furthermore, the lowest mNT titers observed on bus A were equal to the highest mNT titers observed on bus B (Table I). We limited this analysis to persons in the vaccinated group to control for previous immune status). These data suggest that most IgM-negative persons on bus A were recently reinfected with measles.

Comparison of Illness and Infection

None of the 44 participants developed symptoms consistent with classic measles. Between the date of rash onset of the index case and the date of enrollment in the study, 22 persons (50%) developed at least one of the following signs or symptoms: conjunctivitis (5), coryza (6), cough (15), diarrhea (5), fever (10), headaches (15), joint aches (3), swollen lymph nodes (6), photophobia (5), rash (1), sore throat (13), or vomiting (1). The overall rate of illness and rate of individual signs and symptoms did not differ between IgM-positive and IgM-negative persons ($P > .05$ for each). The rates of each sign and symptom remained similar for IgM-positive and IgM-negative persons even after excluding the IgM-negative persons from bus A, who may have been reinfected in the absence of a detectable IgM response ($P > .05$ for each).

DISCUSSION

These results demonstrate that nonclassic measles infections can occur frequently in previously immune populations. In this outbreak, we identified at least ten mild or asymptomatic infections that probably resulted from exposure to a single case (23% of exposed persons). These nonclassic cases occurred both in vaccinated and naturally infected persons (Table I). It is possible that some of the measles-infected persons on the trip were exposed to measles in the community. However, only four classic measles cases, including the index case, were reported from the college out of a student body of about 3,600. Furthermore, persons on bus A, who had longer and more intense exposure to the index case, had higher mNT titers than those on bus B. These data suggest that the bus trip was probably the source of exposure for these infections.

We may have underestimated the number of nonclassic measles infections; many participants on bus A may have been infected in the absence of a detectable

IgM response. We assume that vaccinated persons on both buses had similar mNT prior to the bus trip. Therefore, although we were unable to document infection by showing a diagnostic rise in antibody titers, a recent measles infection among IgM-negative persons on bus A is the most likely explanation for their higher mNT titers compared with similar persons on bus B. The failure to detect an IgM response in some persons on bus A with high mNT titers could indicate a failure to mount an IgM response or that the response had resolved by the time the serum specimens were collected.

Previous studies evaluating nonclassic measles infection make use of a variety of methods, making direct comparisons of rates of nonclassic infections difficult. In a recent study, however, Huiss and colleagues [Huiss et al., 1997] were able to analyze pre- and postexposure sera from 44 parents of children with laboratory-confirmed measles. They detected a greater than fourfold increase in neutralizing antibody titers among only four (9%) of these parents. Moreover, these four parents had the lowest pre-exposure antibody levels. Similar to previous findings of Chen and colleagues [Chen et al., 1990], these data suggest that persons with antibody levels above some threshold do not become re-infected. Huiss's investigation occurred in Germany where measles is still endemic, and persons have the potential for repeated exposures to wild-type measles virus, possibly resulting in higher baseline neutralizing antibody titers. In contrast, it is likely that most persons in our investigation had not been exposed to wild-type measles virus for many years, if ever, so that their antibody titers would not have been repeatedly boosted. If this explanation is correct, one would expect the rate of nonclassic infections to rise as measles control improves in a population.

Persons with nonclassic measles are only epidemiologically important if they transmit measles virus. Several studies have described instances in which measles may have been transmitted from persons with nonclassic infection, but such transmission has not been proven. For example, Edmonson and coworkers [Edmonson et al., 1990] described an outbreak in Wisconsin in which the index case-patient, who had been vaccinated twice previously, failed to meet the clinical case definition because her maximum documented temperature was less than 38.3°C. Second, Reyes et al. [1987] described a case of mild measles in a previously immune person in which measles virus was isolated from peripheral blood mononuclear cells, suggesting systemic infection and therefore the potential for transmission to others. Third, in a district in Greenland in which 92% of the population had been vaccinated with MCV as part of an ongoing study, researchers noted a significant increase in measles titers in two-thirds of the vaccinees in the absence of clinical measles 2–4 years after vaccination, suggesting a silent reintroduction of measles [Pedersen et al., 1989]. We were unable to study measles transmission from nonclassic cases in the current study because most of the contacts of our participants with nonclassic measles had already left the college campus for the summer and were unavailable.

If transmission occurs from nonclassic cases, it probably is not efficient and not able to sustain endemic transmission of measles. Aaby et al. [1986] demonstrated that previously vaccinated persons who develop classic measles infection are less contagious than unvaccinated persons with classic measles. It is possible that measles-infected persons with mild or no symptoms are even less likely to transmit measles; these persons may have better immunity prior to infection and a shorter duration of infection than previously vaccinated persons who develop classic measles. In addition, the absence from 1993 to 1995 of the endemic strain of measles virus that was circulating in the United States between 1989 and 1992 demonstrates that silent transmission of measles did not occur for an extended period [Rota et al., 1996]. If the endemic strain were continuing to be transmitted through nonclassic infections, it should eventually encounter and infect susceptible persons, cause classic cases of measles, and be detected.

In summary, in populations with high levels of immunity to measles, nonclassic measles infections can occur in at least 20% of previously immune persons with close exposure to a person with classic measles. In highly immune populations, these infections may be the most common manifestation of measles infections. Although further study is needed to define better the role nonclassic cases may play in measles transmission, current data suggest that their occurrence will probably not impede efforts to control and eradicate measles.

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